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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/539,677	09/06/2005	C David Pauza	4115-194	7524
23448	7590	05/21/2008	EXAMINER	
INTELLECTUAL PROPERTY / TECHNOLOGY LAW			HUMPHREY, LOUISE WANG ZHIYING	
PO BOX 14329			ART UNIT	PAPER NUMBER
RESEARCH TRIANGLE PARK, NC 27709			1648	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/539,677	PAUZA ET AL.	
	Examiner	Art Unit	
	LOUISE HUMPHREY	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 05 February 2008.
- 2a) This action is **FINAL**. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 3-16,22-28,32,37 and 40 is/are pending in the application.
- 4a) Of the above claim(s) 12-16,22-28,32,37 and 40 is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 3-11 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) All b) Some * c) None of:
1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ . |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>2/20/06,4/5/06,2/28/08</u> . | 6) <input type="checkbox"/> Other: _____ . |

DETAILED ACTION

Claims 1, 2, 17-21, 29-31, 33-36, 38, 39 and 41-45 are cancelled. Claims 3-16, 22-28, 32, 37 and 40 are pending.

Election/Restriction

Applicant's election of Group I, claims 3-11, and the species of Gag carrier protein, in the reply filed on 05 February 2008 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 12-16, 22-28, 32, 37 and 40 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 05 February 2008.

Claims 3-11 are examined.

Priority

Acknowledgement is made of Applicant's claim for priority under 35 U.S.C. §371 to the International Patent Application No. PCT/US2003/040568 on December 18, 2003, which in turn claims priority under 35 U.S.C. 119(e) to United States Provisional Application No. 60/434,368 filed December 18, 2002. In light of the fact that the presently claimed subject matter is fully supported by the disclosure of this U.S.

Provisional Application, benefit to this earlier filed U.S. Provisional Application has been granted. The effective filing date of the instant application is December 18, 2002.

Information Disclosure Statement

Applicant's Information Disclosure Statements (IDS) filed February 02, 2006 (eight pages total), April 05, 2006 (three pages total), and February 28, 2008 (two pages total) have each been received and entered into the application. As reflected by the attached, completed copies of form PTO-1449A (thirteen pages total), the Examiner has considered the cited references.

Claim Rejections - 35 USC § 112, 2nd ¶

The following is a quotation of the second paragraph of 35 U.S.C. §112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 3-11 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 3 recites the phrase "sequences set forth in SEQ ID NO:1..." that is unclear whether the claim encompasses fragments of the recited SEQ ID NO:1-6.

Claims 4-7 are rejected for depending from claim 3.

Claim 8 recites the "from about 15 to about 21 amino acid residues from the amino terminus region of HIV Tat," which is vague and indefinite because the precise amino acids in question are not readily apparent. Due to the error-prone replication of HIV, there are many quasi species with different amino acid sequences. Especially

when insertion or deletion mutations occur during viral replication, the sequences of the quasi species differ substantially from one another that a skilled artisan would not know whether one position number in one strain is referring to the same position in another strain. Therefore, position numbers in the absence of a reference consensus sequence is vague and indefinite. Applicants may amend the claim language to recite a specific reference amino acid sequence to avoid any further confusion or ambiguity. The recitation "wherein the amino acid sequence comprises at least amino acid residue 1, 7 and 12" confounds the meaning of phrase "from about 15 to about 21 amino acid residues from the amino terminus region of HIV Tat." Do applicants mean that the position 1, 7 and 12 would not necessarily be in the about 15 to about 21 amino acid residues from the amino terminus of HIV Tat? Then what are the metes and bounds of the recited "from about 15 to about 21 amino acid residues from the amino terminus region of HIV Tat"?

Claims 9-11 are rejected for depending from claim 8.

Clarification and/or correction are required.

Claim Rejections - 35 USC § 112, 1st ¶, enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 3 and 8-11 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which

was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In making a determination as to whether an application has met the requirements for enablement under 35 U.S.C. 112 ¶ 1, the courts have put forth a series of factors (MPEP §2164.01(a)). See, *In re Wands*, 8 USPQ2d 1400, at 1404 (CAFC 1988); and *Ex Parte Forman*, 230 U.S.P.Q. 546 (BPAI 1986). The factors that may be considered include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *Id.* While it is not essential that every factor be examined in detail, those factors deemed most relevant should be considered.

The nature of invention in claim 3 is a therapeutic composition comprising a fragment of SEQ ID NO:1, 2, 3, 4, 5 or 6, which can be as small as a peptide of three amino acids. The specification provides no guidance on the structure of the immunogenic epitope or the immunogenic effect of a short fragment of less than 15 amino acids. The prior art is remiss of any teachings of such 3-amino-acid therapeutic peptide. It would require undue experimentation to identify fragments of the recited SEQ ID NO. consisting of less than 15 amino acids from the N-terminus that retain the therapeutic characteristics.

The nature of the invention in claims 8-11 is a broadly claimed HIV vaccine composition comprising about 15 to 21 amino acid residues from the amino terminus of the HIV Tat protein, but the specification does not sufficiently support the full scope of the claimed vaccine. The breadth of the claimed invention is exceedingly large and encompasses a vaccine against any HIV strain.

The state of the art is that the term "vaccine", by definition, implies a preparation intended for active immunological prophylaxis. It should also be able to stimulate high titers of neutralizing antibodies. For example, the Illustrated Dictionary of Immunology defines vaccine as a composition that stimulates protective antibodies and T cell immunity and induces active immunity: "A vaccine should stimulate a sufficient number of memory T and B lymphocytes to yield effector T cells and antibody-producing B cells from memory cells. Injection of a vaccine into a non-immune subject induces active immunity against the modified pathogens" (page 613). Prophylaxis is defined as the prevention of disease or of a process that can lead to disease. Although nearly any protein when inoculated can cause an immune reaction, the prophylactic nature of this reaction is not guaranteed and has to be experimentally determined. Given the teachings in the art, it is clear that a compound that merely induces an immune response is not sufficient but must be protective to qualify as a vaccine.

The disclosure fails to provide any working embodiments that meet the claimed limitations. The examples of induction of antibodies by Tat toxoid immunization merely suggests that the amino-terminal 20 amino acids of Tat protein contain immunogenic epitopes, which is far from a validation or prediction of vaccine efficacy. While there is

one example of anti-Tat monoclonal antibody TR1 (against amino acid 1 to 15) and purified IgG from immunized macaques (specification, page 38) neutralizing the transactivation activity of Tat protein in cell culture of CD4⁺ HeLa cells containing a defective provirus, there are no examples of protection against or prevention from the infection of all strains of HIV in an environment that resembles the natural cause of HIV replication/infection. Furthermore, no *in vivo* working example of any challenge studies is disclosed in the specification.

The specification provides little guidance regarding the making and/or using of the claimed vaccine. The specification does not disclose the protective effect, if any, of expressing or delivering the recited Tat peptide in a diseased or uninfected individual. The amount of direction is limited to the generation of natural immune response in rhesus macaques. However, the immune response to Tat-peptide-inoculate is not predictive of the response to all the HIV strains that the vaccinated subject will contract. Besides, there is no teaching of the type and duration of the immune response. Furthermore, there is no challenge study that measures the T cell count and viral load of the test animals before and after a viral challenge. *In vitro* testing is, at most, useful tool for screening potential anti-viral agents but is not predictive of *in vivo* effectiveness. *Ex parte Balzarini* (BdPat App&Int) 21 USPQ2d 1892. One skilled in the art would not associate successful *in vitro* testing results with successful *in vivo* AIDS treatment due to the high level of unpredictability of this art.

The art of HIV vaccine is highly unpredictable, since HIV replicates rapidly with a high mutational frequency and creates diverse 'quasi-species', which are favored by the

Darwinian selective pressures. Therefore, efforts to develop effective treatments and vaccines must overcome the complex evolutionary dynamics in HIV-infected individuals and within affected populations. The consensus seems to be that induction of both humoral and cellular immunity by an HIV-1 vaccine will be required to achieve maximum protection (Tonini, 2005). It is unclear whether there is any CTL response other than neutralizing antibody response. Importantly, two completed efficacy trials conducted by VaxGen using monomeric HIV-1 envelopes resulted in no clear neutralizing responses against relevant primary HIV strains and no protection against infection (Tonini, 2005). Most importantly, macaque models are not considered adequate working models for humans due to unpredictability (Haigwood, 2004) and hence there cannot be direct extrapolation from macaques to humans without clinical evaluation. Still further, it appears highly unlikely that a single construct will protect against all subtypes of HIV-1 (Tonini, 2005). Even when the vaccine strain matches the challenge strain exactly, the HIV protein delivered by plasmid vectors in the immunization failed to protect the monkeys (Desrosiers, 2004). Therefore, the disclosure does not correlate with protection against any strain and/or clade of HIV, especially when the subject may be a person.

Experimental HIV-1 infection *in vivo* and *in vitro* both suffer from the limitation that the *in vitro* amplification of HIV-1, which is required to prepare virus stocks for *in vitro* or *in vivo* infectivity experiments, impose a genetic selection that results in a spectrum of variants present in the clinical specimens used to establish the culture (Kusumi, 1992; Meyerhans, 1989). Because of these uncertainties, and even greater

uncertainties related to the amount of virus transmitted, the site and cell type involved in initial replication, and the kinetics of virus dissemination, the ability of currently available *in vitro* or *in vivo* assays to reliably predict vaccine efficacy is questionable. Small trials in populations with low rates of infection and minimally sized placebo control groups do not have sufficient statistical power to confirm or refute vaccine efficacy.

It is well known in the art that retroviral infections in general, and HIV infections in particular, are refractory to anti-viral therapies. The obstacles to therapy of HIV are well documented in the literature. These obstacles include: i) the extensive genomic diversity and mutation rate associated with the HIV retrovirus, particularly with respect to the gene encoding the envelope protein; 2) the fact that the modes of viral transmission include both virus-infected mononuclear cells, which pass the infecting virus to other cells in a covert manner, as well as via free virus transmission; 3) the existence of a latent form of the virus; 4) the ability of the virus to evade immune responses in the central nervous system due to the blood-brain barrier; and 5) the complexity and variation of the pathology of HIV infection in different individuals. The existence of these obstacles establish that the contemporary knowledge in the art would not allow one skilled in the art to use the claimed invention with a reasonable expectation of success and without undue experimentation, despite the high level of skill in the art. Further, it is well known in the art that individuals infected with HIV produce neutralizing antibodies to the virus, yet these antibodies are not protective and do not prevent the infection from progressing to its lethal conclusion.

The complexities of HIV-1 pathogenesis, the high mutation rate of the viral genome, and its ability to persist in lymphoid and other tissues allow HIV-1 to evade many therapies (Yee, 2001). The immune correlates of viral control in the natural history of HIV disease are unclear and, consequently, the required immune responses to therapeutic vaccination remain elusive (Puls, 2006). A natural immune response, consisting of Tat-epitope-specific antibody response as measured in the instant application, is not effective because HIV has evolved a number of evasion strategies: selection for genetic variants that are antigenic escapes variants; inherent resistance to antibody-mediated neutralization; down regulation of major histocompatibility class I molecules from the surface of infected cells by Nef; and destruction of viral-specific CD4⁺ T helper cells. The main problem with HIV vaccines is that there has not been a solution to overcome the enormous sequence heterogeneity of HIV-1 (see Desrosiers, 2004).

Applicant's specification does not address these factors and does not disclose that the instant invention has overcome these problems. Further, clinical trials using a variety of approaches to vaccinate against HIV-I have not yielded successful results in the treatment and/or prevention of HIV infection. Thus, it is clear, from the state of the art as evidenced by the published literature and the complete lack of working examples in the instant specification, that treating and/or preventing HIV infection by means of vaccines is highly unpredictable and has very little success. Therefore, the quantity of experimentation necessary would be excessive and an undue burden on the artisan.

Applicants have not provided sufficient guidance to allow one skilled in the art to make and use the claimed invention with a reasonable expectation of success and without undue experimentation. A therapeutic HIV vaccine comprising a recombinant Tat peptide is not routine in the art, and rather, is considered as problematic and challenging for development. Without sufficient guidance to elicit therapeutic protection against HIV, the experimentation left to those skilled in the art is undue or unreasonable under the circumstances. While Applicant is not required to set forth working examples, the specification must set forth sufficient teachings to allow one to make and use the claimed invention. There is no evidence that the claimed peptides will actually be suitable for vaccinating against HIV. Thus, the instant specification, based on the evidence as a whole, in light of the factors articulated by the court in *In re Wands*, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. §103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 3-7 are rejected under 35 U.S.C. §103(a) as being unpatentable over Frankel *et al.* (US 5,652,122, 29 July 1997).

Claim 3 is drawn to a therapeutic composition comprising at least one peptide having an amino acid sequence consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5 or SEQ ID NO:6. Claims 4-6 further limit the composition to the peptide conjugated to a HIV carrier protein. Claim 7 further limits the composition to comprise a pharmaceutically acceptable carrier.

Frankel *et al.* discloses a composition comprising a pharmaceutically acceptable carrier and a molecule of interest-Tat protein conjugate. The molecule of interest can be an antigen from the bacteria or virus or other infectious agent that the vaccine is to immunize against (e.g. gp120 of HIV) (column 10, line 57-66). The Tat protein, acting as a transport polypeptide, can be a variant consisting of Tat amino acids (aa) 1-21 fused directly to Tat amino acids 38-72 (column 10, line 13-15; column 40, line 45-47). According to the sequence listed in column 57-58 (SEQ ID NO:7), the Tat amino acids 1-21 match the instantly claimed SEQ ID NO:1 and SEQ ID NO:5. The transport peptides may be advantageously attached to cargo molecules by chemical cross-linking or by genetic fusion (column 3, line 52-54).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the Tat aa1-21 peptide with the HIV Env protein, gp120, as suggested by Frankel *et al.* The skilled artisan would have been motivated to transport any cargo polypeptide, such as HIV Env gp120, by conjugating the cargo with the aa1-21 Tat peptide, so as to avoid the problems of spurious trans-activation and disulfide aggregation, while the reduced size of the Tat peptide, as compared to the full size Tat protein, minimizes interference with the biological activity of the cargo

molecules (abstract). Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

No claim is allowable.

Applicant is reminded that any amendment must point to a basis in the specification so as not to add new matter. See MPEP §714.02 and §2163.06.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louise Humphrey, Ph.D. whose telephone number is 571-272-5543. The examiner can normally be reached on Mon-Fri, 9:30 am - 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a

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USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/L. H./
Examiner, Art Unit 1648

/Bruce Campell/
Supervisory Patent Examiner, Art Unit 1648